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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/918,187	07/30/2001	Rosanne M. Crooke	ISPH-0590	2706

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EXAMINER	
LACOURCIERE, KAREN A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 10/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/918,187	CROOKE ET AL.	
	Examiner	Art Unit	
	Karen A. Lacourciere	1635	

-- Th MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-7,9,10,12-15 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-7,9,10,12-15 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The rejection of record of claims 15-20 under 35 U.S.C. 112, first paragraph, is withdrawn in response to Applicant's amendments filed 08-04-2003.

Claim Rejections - 35 USC § 102

The rejections of record of claims 1, 2, 11, 12 and 14 under 35 USC 102 as anticipated by Stenn et al. or Prouty et al. are withdrawn in response to Applicant's amendments filed 08-04-2003, however, new rejections under 35 USC 102 are set forth herein.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

Claims 1, 4, 5, 6, 7, 9, 10, 12, 13, 14 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Damha et al. (WO 99/67378).

Damha et al. disclose and claim antisense compounds comprising a modified base, including a 5-methylcytosine, and further comprising modified backbones, including phosphorothioate, and modified sugar residues, including 2'-O-methoxyethyl. Damha et al. disclose these oligonucleotides in a composition comprising a pharmaceutically acceptable diluent (e.g. water) and compositions encompassed in the term colloidal dispersion systems, e.g. liposomes and wherein the antisense is chimeric. Damha et al. disclose contacting cells in vitro with this antisense oligonucleotide. Damha et al. disclose such antisense oligonucleotides wherein the oligonucleotide comprises a sequence with 15 residues fully complementary to residues 4501-4515 and residues 5207-5221 of SEQ ID NO:3 (see for example SEQ ID NO:2 of Damha et al.). Damha et al. do not explicitly disclose SEQ ID NO:2 as targeting human stearoyl-CoA desaturase and inhibiting the expression at least 10%, however, based on the breadth of language "specifically hybridize" in the claim, the oligonucleotide disclosed by Damha et al. meets all of the structural limitations of the claimed antisense compounds, since the sequence of the prior art oligo matches with 100% identity to 15 residues within SEQ ID NO:3, and is within the recited size requirement for the claimed oligo. Accordingly, the oligonucleotide disclosed by Damha et al. would specifically hybridize as claimed. The burden of establishing whether the prior art oligos has the further function of inhibiting gene expression at least 10%as claimed falls to applicant. See (*In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433-434 (CCPA 1977): "Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an

applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product... Whether the rejection is based on 'inherency' under 35 USC 102, on 'prima facie obviousness' under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products [footnote omitted]. See also MPEP 2112: "[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112 citing *In re Fitzgerald* 205 USPQ 594, 596 (CCPA 1980), quoting *In re Best* 195 USPQ 430 as per above.

Therefore, Damha et al. anticipates claims 1, 4, 5, 6, 7, 9, 10, 12, 13, 14 and 15.

Claims 1, 4, 5, 6, 10, 12, 13, 14, 15 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Beigelman et al. (WO 96/18736).

Beigelman et al. disclose ribozymes, which are encompassed within the term antisense oligonucleotides, wherein the hybridizing region of the ribozyme comprises a sequence fully complementary to residues 1404-1417 of SEQ ID NO:3 (see for example SEQ ID NO:1777 of Beigelman et al.). Beigelman et al. further disclose their ribozymes as comprising modified backbones, including for example, phosphorothioate, and modified bases and sugars and wherein the ribozymes are chimeric. Beigelman et al. disclose their oligonucleotides in a composition comprising a pharmaceutically acceptable diluent, e.g. water, and a colloidal dispersion system, e.g. liposomes. The full length of the ribozyme is disclosed as within the range of 8-50 nucleobases and

wherein the length is greater than 30 (e.g. 40 nucleotides). Beigelman et al. disclose wherein cells in vitro are contacted with the claimed ribozyme.

Beigelman et al. do not explicitly disclose their ribozymes as targeting human stearoyl-CoA desaturase and inhibiting the expression at least 10%, however, based on the breadth of language "specifically hybridize" in the claim, the oligonucleotides disclosed by Beigelman et al. meet all of the structural limitations of the claimed antisense compounds, since the sequence of the prior art oligo matches with 100% identity to 14 residues within SEQ ID NO:3, and is within the recited size requirement for the claimed oligo. Accordingly, the oligonucleotide disclosed by Beigelman et al. would specifically hybridize as claimed. The burden of establishing whether the prior art oligos has the further function of inhibiting gene expression at least 10% as claimed falls to applicant. See (*In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433-434 (CCPA 1977): "Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product... Whether the rejection is based on 'inherency' under 35 USC 102, on 'prima facie obviousness' under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products [footnote omitted]. See also MPEP 2112: "[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of

his [her] claimed product." The MPEP at 2112 citing *In re Fitzgerald* 205 USPQ 594, 596 (CCPA 1980), quoting *In re Best* 195 USPQ 430 as per above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4-7, 9, 10, and 12-15 are maintained as rejected and claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Stenn et al. (WO 00/09754, cited on PTO form 1449, filed June 4, 2002) in view of Milner et al. and Baracchini et al. (US Patent No. 5,801,154), for the reasons of record set forth in the prior Office action (mailed 01-13-2003).

Claims 1, 4-7, 9, 10, 12-15 and 21 are drawn to an antisense oligonucleotide 8-50 nucleotides in length targeted to a nucleic acid encoding human stearoyl-CoA desaturase, wherein the antisense comprises at least one modified base, including 5-methylcytosine modification, modified sugars, including 2'-O-methoxyethyl modifications, internucleoside linkage modifications, including phosphorothioate, chimeric antisense, and compositions comprising said antisense and a pharmaceutically acceptable carrier, including a colloidal dispersion system. The claims are further drawn to methods to inhibit the expression of human stearoyl-CoA desaturase in cells *in vitro*.

Stenn et al. teaches inhibiting the expression of human stearoyl-CoA desaturase using antisense expressed from a vector and teaches the full length sequence of a nucleic acid encoding human stearoyl-CoA desaturase, wherein the nucleic acid comprises SEQ ID NO:3 of the instant application (see, for example, figures 8 and 9 of Stenn et al.). Stenn et al. do not teach antisense targeted to a nucleic acid encoding human stearoyl-CoA desaturase of a length 8-50 nucleobases long. Stenn et al. do not teach antisense targeted to a nucleic acid encoding human stearoyl-CoA desaturase wherein the antisense comprises a modified base, including a 5-methylcytosine modified base, a modified backbone, a modified sugar, or chimeric antisense molecules. Stenn et al. teaches that it is preferable to screen for agents that inhibit the expression of human stearoyl-CoA desaturase by greater than 50%.

Baracchini et al. teach incorporating a modified base into antisense and backbone modifications for antisense, including phosphorothioate modifications, 2'-O-

methoxyethyl sugar modifications, 5-methyl cytosine base modifications, chimeric oligonucleotides and modified internucleoside linkages, including phosphorothioate linkages, to increase antisense stability and enhance affinity and antisense oligonucleotides of 8-30 nucleotides in length. Baracchini et al. further teach pharmaceutical carriers and colloidal dispersion systems (for example liposomes) for use in delivery of antisense compounds.

Milner et al. teach methods of screening for determining antisense targeted to any known gene.

It would have been obvious to one of ordinary skill in the art to modify the vector expressed an antisense oligonucleotides targeted to a nucleic acid encoding human stearoyl-CoA desaturase, as taught by Stenn et al., by making antisense a length within the range of 8-50 nucleobases (as taught by Baracchini et al.), because antisense of a short length are more easily synthesized and easier to deliver to cells and antisense of this length is conventional in the art. It would have been obvious to synthesize such antisense with a modified base because modified bases were well know in the art as a means to improve the hybridization of an antisense molecule to its target nucleic acid, as exemplified by Baracchini et al. It would have been further obvious to make said antisense comprising modifications, including 2'-O-methoxyethyl, 5-methyl cytosine, chimeric oligonucleotides and modified internucleoside linkages, including phosphorothioate linkages, as taught by Baracchini et al., because such modifications were routine and well known in the art as modifications which enhance the stability, uptake and affinity of an antisense molecule (see for example Baracchini et al. column

6, paragraph 3). It would have been obvious to one of ordinary skill in the art to make a composition comprising said antisense and a pharmaceutically acceptable carrier, including a colloidal dispersion system, because pharmaceutically acceptable carriers, including colloidal dispersion systems (e.g. liposomes) were well known in the art for use with antisense molecules as a means to deliver antisense molecules to cells *in vitro* (cell culture), as evidenced by Baracchini et al., and because Stenn et al. teach antisense expressed from a vector targeted to human stearoyl-CoA desaturase in compositions comprising a pharmaceutically acceptable carrier (see for example Stenn et al. page 16) for use, for example, in topically administered antisense.

One skilled in the art would have been motivated to make an antisense molecule targeted to a nucleic acid encoding human stearoyl-CoA desaturase because Stenn et al. teach inhibiting human stearoyl-CoA desaturase using antisense and one of ordinary skill in the art would be motivated to make such antisense of a length within the range of 8-50 nucleobases, including wherein the oligonucleotide is greater than 30 nucleobases, for ease of synthesis and delivery and because it is conventional in the art to make antisense within this range (as exemplified by Baracchini et al.). Increasing the length to greater than 30 nucleotides would have been an obvious manes to increase specificity of the oligonucleotide. One of ordinary skill in the art would have been motivated to incorporate the modifications taught by Baracchini et al. for the benefits of stability and improved hybridization. The skilled artisan would have been motivated to screen for antisense which inhibit to a level greater than 10%, because Stenn et al. teach that it is preferable to screen to find agents that inhibit expression at least 50%.

One skilled in the art would have expected to be able to find antisense which inhibits the expression of human stearoyl-CoA desaturase because the sequence of nucleic acids encoding human stearoyl-CoA desaturase, including SEQ ID NO:3 of the instant application, were known in the art and methods of screening for antisense to a known gene was routine (see for example Milner). The skilled artisan would have expected to find an antisense that inhibits the expression of human stearoyl-CoA desaturase by at least 10% under some conditions because that level of inhibition is relatively low. As exemplified by Baracchini et al. and Milner et al. screening the full length of a target gene yields many antisense sequences, which inhibit the expression of a target gene to varying degrees, often decreasing expression levels much greater than 10% (see table I of Baracchini et al. for example), particularly when the antisense oligonucleotide has been modified by incorporating modifications.

It would have been obvious to one of ordinary skill in the art to use antisense targeted to a nucleic acid encoding human stearoyl-CoA desaturase in a method of inhibiting the expression of human stearoyl-CoA desaturase in cells *in vitro* (cell culture), because it would be an obvious use for an antisense molecule designed to hybridize to and inhibit the expression of a nucleic acid encoding human stearoyl-CoA desaturase.

Therefore, the invention of claims 1, 4-7, 9, 10, 12-15 and 21 would have been obvious to one of ordinary skill in the art, as a whole, at the time the instant invention was made.

Response to Arguments

Applicant's arguments filed 08-04-2003 have been fully considered but they are not persuasive.

In response to the rejection of record of claims 1, 2 and 4-15 set forth in the prior Office action, Applicant argues that the claimed compounds and methods are not obvious because the cited references do not meet all of the limitations of the claims, specifically, the claimed compounds are required to have inhibitory activity. Applicant argues that Stenn et al. teaches a primer sequence and teaches screening for an "agent" that increases or decreases expression levels of SCD, but does not describe that agent beyond an antibody. Applicant argues that Stenn et al. only makes reference to antisense in the context of a vector expressed antisense sequence, which is not the type of antisense encompassed by the claims, given that the expressed antisense described by Stenn et al. is not synthetic. Applicant argues Stenn et al. do not teach synthetic antisense that inhibit by at least 10%. These arguments are not found to be persuasive because the primer sequence taught by Stenn et al. is not the aspect of Stenn et al. applied in the rejection under 35 USC 103(a), rather it was only applied in the rejection under 35 USC 102, which has been withdrawn. Stenn et al. has been relied upon as teaching inhibition of human stearoyl-CoA desaturase using antisense, and for teaching screening for agents that inhibit the expression of human stearoyl-CoA desaturase by greater than 10%. Although Stenn et al. makes reference to an antibody as a means to inhibit the activity of human stearoyl-CoA desaturase, Stenn et al. teaches screening for agents that inhibit the expression of a nucleic acid encoding

human stearoyl-CoA desaturase. Stenn et al. do not exclude antisense agents, nor do they teach antibodies as a preferred embodiment for inhibiting the expression. The one exemplified embodiment of Stenn et al. for inhibition of expression is via antisense, further, antisense was well known in the art as a preferred means to inhibit expression of a target gene (as exemplified in the teachings of the secondary references) and it would have been an obvious choice of an agent to use in the methods taught by Stenn et al. Although Stenn et al. teach inhibition of human stearoyl-CoA desaturase using a vector expressed antisense molecule, it would have been obvious to substitute the vector expressed antisense molecule for a shorter, synthetic, modified antisense, because antisense of this type was well known in the art and taught as providing the benefits of improved cellular stability and improved hybridization, making this type of antisense an obvious choice for the inhibitory agents taught by Stenn et al.

Applicant argues that the secondary references do not make up for the deficiencies of Stenn et al. because Baracchini et al. does not make reference to the same target gene and does not teach the vector expressed antisense taught by Stenn et al. and Milner et al. is general, does not teach antisense targeted to human stearoyl-CoA desaturase that inhibit by at least 10%, and does not make reference to the vector expressed antisense taught by Stenn et al.

These arguments are not persuasive because Baracchini et al. and Milner et al. are not relied upon to teach targeting human stearoyl-CoA desaturase, but rather demonstrate that modified antisense, as claimed, was well known in the art at the time

of the invention and, further, that methods of making and screening for antisense were well known in the art at the time of the invention.

Applicant argues that the combination of references only meet the standard of "obvious to try", which is not the appropriate standard to determine patentability. This is not found to be persuasive because the methods of screening for antisense sequences known in the art were routine and decreasing expression of a target gene by at least 10% is not a high level of inhibition. Stenn et al. clearly sets forth a reasonable expectation that screening will provide agents that inhibit expression by an even higher level (i.e. greater than 50%) and provides an embodiment of antisense that inhibits to greater than 10%, although it is a vector expressed antisense, the skilled artisan would reasonably expect to find antisense of a synthetic nature that would also inhibit to that degree, similar to the vector expressed antisense.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Lacourciere whose telephone number is (703) 308-7523. The examiner can normally be reached on Monday-Thursday 7:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-1935 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Karen A. Lacourciere
October 20, 2003

KAREN A. LACOURCIERE, PH.D
PRIMARY EXAMINER